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Familial Mediterranean Fever in Canada

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FAMILIAL Mediterranean fever (FMF) has received extensive attention in the medical literature of the past decade. Most of the reports come from Israel, where over 400 cases have been studied.[1] Smaller groups have been reported from France, the United States and elsewhere, but none hitherto from Canada, so that we are prompted to report three cases which we have observed in Montreal.

It is likely that more cases will now be found here, for in the last 12 years Canada has acquired about 30,000 people, mostly in Quebec and Ontario, who are genetically at risk for FMF. Since this is an autosomal recessive condition and is said to occur once in 2720 persons of the susceptible group,[1] another seven or eight cases can be expected. The incidence of FMF is largely restricted to two ethnic groups, Sephardic Jews and Armenians. Both of these groups have been hitherto little known in Canada, but during the past twelve years some 10,000 Sephardic Jews have come here from North Africa. They are descendants of Jews expelled from Spain by the Inquisition, many of whom then settled in North Africa, and thereafter had little contact with the European Jews. During recent political upheavals most of them emigrated to Israel, France and Canada, chiefly to Quebec, since they are French-speaking.[2] The majority of Canadian Jews are Ashkenazim; that is, they have come to this country from Germany and Eastern Europe.

During the same period the Armenian population of Montreal has grown from 1000 to 10,000, and that of Canada to 20,000, as part of the emigration from Greece and to a lesser extent from Turkey and Egypt.[3]

It is these two groups of New Canadians who present us with this hitherto unfamiliar and still rare clinical entity, familial Mediterranean fever.

CASE REPORTS

CASE 1.—This 7-year-old boy of Sephardic Jewish stock came to Canada from Tunisia in August 1958. He had a history of recurrent fever and leg pain going back to early childhood and had been investigated in France when 4 years old because of a three-day illness with fever and painful ankles. At 5 years of age he had recurrent attacks of fever, abdominal pain and limb pain as often as twice a month. At the age of 6 he spent one month in a Tunisian hospital where the diagnosis was acute rheumatic fever (ARF) without cardiac involvement; he received steroids and antibiotics. During the following year he had an estimated 30 separate attacks of fever, abdominal pain and limb pain. When he first presented at the medical clinic of the Montreal Children's Hospital in September 1958, his examiners noted his dental caries, flat feet and Duane's syndrome, but were unable to make a diagnosis. On October 22, 1958, he developed severe abdominal pain and was admitted to hospital. He was found to have a rigid, tender abdomen and a leukocytosis, and an appendectomy was performed. The surgeon described the appendix as acutely inflamed; the pathologist, however, reported acute periappendicitis.

Following several clinic visits for arthralgia, arthritis, low-grade fever and abdominal pain, he was readmitted on January 28, 1959. At that time his ESR fluctuated widely, dropping in three days from 40 mm. in one hour to 9 mm. The antistreptolysin "O" titre was below 100 units per ml. There was no consistent response to acetylsalicylic acid. No satisfactory diagnosis was made, but it was believed that acute rheumatic fever could be excluded. He had three admissions to the Jewish General Hospital during the next year, one for an attack of abdominal pain of undetermined etiology, one for possible osteomyelitis of the right thumb, with transient periosteal changes on radiography, and one for undiagnosed joint pain, fever and abdominal pain. Frequent clinic visits for similar complaints continued. When he was 8 years of age, he was readmitted to the Montreal Children's Hospital for intensive investigation. He had just recovered from a four-day illness with fever and abdominal pain and by then felt well and appeared to be in good general condition. He was found to have a slightly enlarged spleen. His ESR was 37 mm. in one hour, falling to 1 mm. three weeks later. Many investigative procedures were carried out, including urinalysis, hemogram, blood and urine cultures, intravenous pyelography, bone marrow examination, blood fibrinogen, urine porphyrins, differential agglutinations and LE preparation, all of which were normal. A diagnosis of FMF was then entertained for the first time. Soon afterwards the parents heard that their 11-year-old nephew, still in Tunisia, had been assigned the same diagnosis there. The nephew is of consanguineous parentage.

Attacks of arthritis, fever and abdominal pain, combined or separate and lasting one to four days, continued. In 1962 the boy was readmitted. Intravenous pyelography on this occasion demonstrated

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slight enlargement of the kidneys. Because of this and the slight splenomegaly, amyloidosis was suspected. However, there was no albuminuria, and a Congo red test and renal function tests were normal. Percutaneous renal biopsy yielded only four glomeruli, but these showed no amyloid deposit or other abnormality. Urine etiocholanolone and blood lipids were normal. A rectal biopsy, done later in search of amyloid, was also negative. A three-day challenge of a high-fat diet was followed directly by an attack of fever, abdominal pain and nausea. The boy was then discharged with a diagnosis of FMF and advised to follow a low-fat diet. This he did for four months, with marked reduction in the frequency and severity of attacks. Subsequent relaxation of the diet brought more attacks. Reinvestigation in 1967 yielded no change in the diagnosis and no evidence of amyloidosis. In addition to his somatic complaints the boy, now aged 17, has become depressed.

CASE 2.—A 4½-year-old girl had abdominal pain and low-grade fever on three or four occasions during the preceding year. On no occasion were these symptoms severe enough to warrant medical attention. She is the child of Sephardic Jews who came to Montreal from Morocco. She presented with severe abdominal pain of six hours' duration and a rectal temperature of 100° F. There were no other symptoms. The pain was constant and mainly periumbilical. Physical examination revealed a well-nourished, well-developed 4-year-old girl in moderate distress. There was slight generalized tenderness and voluntary guarding, but no rebound tenderness. Rectal examination was negative. Blood pressure was 100/60. The white blood count was 10,400; urinalysis was normal. The pain and fever subsided in 12 hours with no medication.

After two similar attacks in the ensuing two months, FMF was suspected; she was admitted to hospital to rule out other causes of abdominal pain and fever. Laboratory results were as follows: A urine culture showed no growth. Intravenous pyelogram and barium enema were normal. Electrophoresis of serum proteins revealed an elevated alpha-2 globulin to 1.07% (normal: 0.4-0.8%) but was otherwise normal. The hemoglobin was 12.0 g.; the leukocyte count was 14,300 with 89% polymorphonuclears, 7% lymphocytes, 3% monocytes and 1% metamyelocytes. The ESR was 29 mm. in one hour; the platelets were normal in a smear. Fasting blood sugar was 72 mg. per 100 ml. and the BUN was 11 mg. per 100 ml. The urine gave a negative result when tested for coproporphyrins and uroporphyrins. Familial Mediterranean fever was strongly suspected on the basis of the patient's ethnic origin, the recurrent attacks of fever with abdominal pain and the exclusion of other diagnoses by detailed investigation.

CASE 3.—The 3-year-old brother of Case 1 presented with joint pain and fever two months after his sibling was suspected of having FMF. He had been seen by another physician one year previously for similar complaints. A diagnosis of rheumatic fever was made at that time but later rejected when the symptoms disappeared in 24 hours without therapy. Since then he had experienced several episodes of redness and swelling of the ankles with low-grade fever; each of these terminated within 12 to 48 hours without therapy.

Physical examination revealed swelling, tenderness, redness and limitation of movement of the left ankle. The rectal temperature was 100° F. There were no heart murmur, skin rash, chorea or subcutaneous nodules. The Hb. was 11.3 g. per 100 ml., the corrected ESR was 24 mm. in one hour and the leukocyte count was 8200 with a normal differential. Platelets in a smear were normal. The serum protein electrophoresis was normal, as was the serum fibrinogen. The antistreptolysin "O" titre was less than 100 units per ml.

The joint pain, swelling and limitation of movement disappeared within 24 hours without therapy. A diagnosis of familial Mediterranean fever was made on the basis of recurrent attacks of fever and joint manifestations, the ethnic origin, the family history, and the absence of other causative factors capable of explaining the clinical picture. Since that time the child has experienced attacks of self-limited abdominal pain and fever on several occasions.

DISCUSSION

Familial Mediterranean fever may declare itself at any time between early childhood and young adult life. Once manifest, it continues for the individual's lifetime. It is characterized by self-limited episodes of illness lasting an average of 48 hours and recurring after an unpredictable interval. These are essentially episodes of serositis: fever is invariably present, painful swelling of one or more joints may occur, and there may be a tender rigid abdomen and chest pain. The synovitis, peritonitis and pleuritis may occur separately or in any combination or sequence. Pericarditis occurs very rarely.[4] All of the manifestations of serositis, including the elevated sedimentation rate, are rapidly and remarkably reversible (with the minor exception of an infrequently observed long-standing mono-arthritis). However, 40% of presently known patients are affected by an associated condition which is irreversible and of grave prognostic import, namely amyloidosis. This may appear at any stage of the illness, indicated usually by albuminuria; it is progressive and may be expected to lead to death from renal failure within 10 years of becoming manifest.

The etiology of FMF is unknown. Several theories have been proposed. Bondy, Cohn and Castiglione[6] found elevated etiocholanolone levels in some patients with FMF, but this

change has not been confirmed in the Israeli patients. Mellinkoff and his associates[7] have described elevation of serum glycoprotein levels in patients with FMF and also in their relatives. The significance of this finding has yet to be established.

The ethnic background of FMF is remarkably restricted. The gene frequency has been worked out with precision for the Sephardic Jews in Israel[1] but not yet for Armenians, who may not necessarily have the same gene frequency.

Since there is no diagnostic test for FMF, the diagnosis is a clinical one, based on six features: fever, serositis, amyloidosis, ethnic background, family history and exclusion of other possibilities. The clinical picture of periodic serositis described above, especially but not necessarily accompanied by amyloidosis, will suggest the diagnosis of FMF if the patient is an Armenian or a Sephardic Jew. (In other ethnic groups the condition is very rare but does occur and may be considered if other criteria are met.) A positive family history consistent with the autosomal mode of inheritance found in FMF will strongly support such a diagnosis. Finally, other diagnostic possibilities must be methodically ruled out, for in the last analysis the diagnosis is one of exclusion.

Our patients satisfy five criteria but do not yet show amyloidosis. Our first patient (who was, we believe, the first patient with FMF to be found in Canada) illustrates very well the diagnostic pitfalls set for the unwary by this condition: the arthritis which is not a collagen disease, the peritonitis which does not call for operative intervention.

Our first patient was managed with a low-fat diet which afforded temporary improvement; this was tried after one group of investigators in California reported a sharp reduction in frequency and severity of attacks when FMF patients were limited to 20 g. of saturated fat daily.[5, 7] Their results seemed convincing although they were based on a small number of patients. That they are not confirmed by the Israeli investigators, who have so many more patients for study, is disappointing and rather puzzling. The Israeli physicians mention the threat to emotional stability posed by this chronic illness in the absence of effective therapy and with the risk of amyloidosis. Our first patient is becoming depressed to a degree that concerns us, and we are aware of an adolescent girl with FMF in Montreal undergoing psychotherapy for a similar problem.

Summary Three children in Montreal are described who were found to have familial Mediterranean fever. This condition which is inherited as an autosomal recessive trait has a remarkably restricted ethnic distribution, being confined largely to Sephardic Jews and Armenians. Hitherto unfamiliar, this illness may now be encountered in Canada where moderate immigration from both of these groups has occurred during the past decade. This diagnosis should be considered in patients who suffer from recurrent self-limited episodes of illness and meet most of these six criteria: fever, serositis (synovitis, pleuritis, peritonitis), positive family history, expected ethnic background, exclusion of other diagnostic possibilities and amyloidosis. All manifestations of the disease are recurrent and reversible except for amyloidosis, which affects 40% of known patients, presents usually as albuminuria, and progresses to death from renal failure within 10 years of its detection. No effective treatment has been found.

Résumé Les auteurs présentent trois cas de maladie périodique familiale découverts chez trois enfants de Montréal. Cette pathologie qui est héréditaire selon le mode récessif frappe des ethnies remarquablement limitées: on ne la rencontre généralement que chez des Juifs séphardiques et des Arméniens. Jusqu'alors peu connue, cette maladie se rencontre désormais au Canada où a eu lieu une immigration modérée de représentants de ces deux groupes pendant la dernière décennie. On devra envisager ce diagnostic chez les malades qui présentent des épisodes récidivants mais limités de la maladie et qui répondent généralement aux six critères suivants: fièvre, sérosité (synovite, pleurite, péritonite), antécédents familiaux, antécédents ethniques classiques, exclusion d'autres diagnostics possibles et amyloïdose. Tous les symptômes de la maladie sont sujets à récidives et sont réversibles, à l'exception de l'amyloïdose qui touche près de 40% des cas connus, et qui se traduit habituellement par de l'albuminurie et évolue vers une issue fatale par insuffisance rénale dans la période de 10 ans qui suit sa découverte. Jusqu'ici, aucun traitement n'est efficace.

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REFERENCES

1. SOHAR, E. *et al.*: *Amer. J. Med.*, **43**: 227, 1967.
2. Jewish Immigrant Aid Services of Canada: Personal communication.
3. Canadian Armenian Congress: Personal communication.
4. RAVIV, U., RUBINSTEIN, A. AND SCHONFELD, A. E.: *Amer. J. Dis. Child.*, **116**: 442, 1968.
5. MELLINKOFF, S. M., SCHWABE, A. D. AND LAWRENCE, J. S.: *Trans. Ass. Amer. Physicians*, **73**: 197, 1960.
6. BONDY, P. K., COHN, G. L. AND CASTIGLIONE, C.: *Ibid.*, **73**: 186, 1960.
7. MELLINKOFF, S. M. *et al.*: *Ann. Intern. Med.*, **56**: 171, 1962.